Sponsor Novartis
Generic Drug Name Certoparin
Therapeutic Area of Trial Thrombosis prophylaxis
Approved Indication According to the German SPC: - Primary prophylaxis of deep vein thrombosis (DVT) in peri- or postoperative patients with medium or high risk of DVT and in patients with acute ischemic stroke. - Therapy of an acute DVT.
Study Number CMEX839BDE02
Title An open-label comparison of the efficacy and safety of the low-molecular-weight heparin Certoparin (3000 U anti-Xa once daily) with unfractionated heparin for the prevention of thromboembolic complications in acutely ill non-surgical patients
Phase of Development Phase III
Study Start/End Dates 24 Feb 2006 to 12 Dec 2007

Study Design/Methodology

This was a randomized, open-label, multi-center prospective comparative parallel-group study to investigate efficacy and safety of a single daily dose of 3000 U anti Xa of Certoparin when compared to 7500 IU of unfractionated heparin (UFH) administered twice daily during the treatment period of 10±2 days in non-surgical acutely ill hospitalized patients.

Centres

28 centers in Germany

Publication

Not yet submitted

Objectives

Primary objective(s)

The primary objective of this clinical study was to evaluate the efficacy of the low molecular weight heparin (LMWH) Certoparin in acutely ill, immobilized, non-surgical patients by testing the hypothesis that a single daily dose of 3000 U anti Xa of Certoparin was non-inferior in preventing venous thromboembolism (VTE) when compared to 7500 IU of unfractionated heparin (UFH) administered twice daily during the treatment period of 10±2 days, based on a composite endpoint consisting of asymptomatic or symptomatic proximal or distal deep vein thrombosis (DVT), symptomatic pulmonary embolism (PE) or death related to VTE.

Secondary objective(s)

The secondary objective of this clinical study was to explore the safety of Certoparin during the treatment period, as well as to estimate the risks for each of the individual components of the composite endpoint (symptomatic VTE) and the incidence of hemorrhage during the follow up period of 3 months.

Test Product (s), Dose(s), and Mode(s) of Administration

Investigational drug
- Active agent: Certoparin-sodium

Formulation: solution for subcutaneous injection in prefilled syringes, Unit dose: 3000 U anti Xa of Certoparin.

Reference Product(s), Dose(s), and Mode(s) of Administration

Active agent: unfractionated Heparin (Liquemin® N 7500)

Formulation: solution for subcutaneous injection in prefilled syringes, Unit dose: 7500 IU of UFH

Criteria for Evaluation

Primary variables

The occurrence of thromboembolic events (proximal or distal DVT, PE or VTE related death) during treatment.
The objective findings of the ultrasonographic examination, adjudicated by a Central Endpoint Adjudication Committee.

Secondary variables

Thromboembolic events during follow-up period of 3 months.

Safety and tolerability

(1) Safety endpoints occurring during the treatment period:
- Hemorrhage (major or minor)
- Thrombocytopenia
- Symptomatic HIT type II
- Induction of HIT-II specific antibodies

Pharmacology

None.

Other

None

Statistical Methods

The sample size calculation is based on the one-sided equivalence test with normal approximation. The primary objective of the study is the incidence of thromboembolic complications. The non-inferiority margin δ was predefined to be 4%.

The parameters used for calculation were as follows:

p1 = 0.07, p2 = 0.065, α = 0.025 (one-sided significance level of the statistical test), β = 0.20 (corresponding to power of 80 %), δ = 0.04 (amplitude of the one-sided equivalence area).

(p1: probability for the occurrence of thromboembolic complications in the unfractionated heparin (UFH) group; p2: probability for the occurrence of thromboembolic complications in the low-molecular-weight heparin Certoparin group).

The non-inferiority margin δ was predefined to be 4%.

In accordance with the above criteria a sample size of 488 patients per group was calculated using the software N-Query Advisor.

Taking drop-outs into account, a total of 1200 patients (600 in each group) were planned for enrollment to provide the adequate power for the statistical analysis.

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria

- Male and female patients over 40 years of age
- Hospitalization due to an acute non-surgical disease
- Significant decrease in mobility (i.e. patient is completely bedridden or patient can only walk short distances with the support of a nurse) as compared to the condition before the onset of the acute disease
- Written informed consent

Main exclusion criteria

- Indication for anticoagulant or thrombolytic therapy
- Major surgical or invasive procedure within the 4 weeks that precede randomization
- Expected major surgical or invasive procedure (including spinal/peridural/epidural anesthesia or lumbar puncture) within the 2 weeks that follow the randomization
- Immobilization due to cast or fracture of lower extremity
- Immobilization lasting longer than 3 days in the period prior to randomization
- Heparin administration longer than 36 hours in the period prior to randomization
- Acute ischemic stroke
- Hemorrhagic stroke or other intracranial bleeding (acute or within the last 12 months)
- History of or current intracranial disease (e.g. cerebral aneurysma)
- Injury to or operation on central nervous system, eye, or ear
- Uncontrolled hypertension (diastolic blood pressure > 105 mm Hg)
- Life expectancy < 1 year
- Prothrombin ratio < 60 % or international normalized ratio (INR) >1.5; aPTT > 1.5 fold ULN
- Active peptic ulcer
- Active major bleeding within the last 4 weeks
- Hemorrhagic diathesis
- Lack of coagulation factors
- Endocarditis
- History of or current heparin-induced thrombocytopenia type II
- Known hypersensitivity to any of the study drugs or to drugs with similar chemical structures
- Retinopathy, intravitreal, or other intraocular hemorrhage
- Abortus imminens
- Platelet count <100000/µl
- Severe renal disease (Creatinine > 180 µmol/l)
- Hepatic disease (ALAT >3 fold ULN)
- Pancreatic diseases with enhanced risk of bleeding
- Suspicion of malignant tumor with enhanced risk of bleeding
- Renal or ureteral calculus

Number of Subjects

	Certoparin	UFH
Planned N	600	600
Randomised* n	163	174
Intent-to-treat population (ITT) n (%)**	103 (63.2)	100 (57.5)
Completed n (%)	137 (84.0)	124 (71.3)
Withdrawn n (%)	26 (16.0)	48 (27.6)
Withdrawn due to adverse events n (%)	4 (2.5)	9 (5.2)
Withdrawn due to lack of efficacy n (%)	0	0
Withdrawn for other reasons including death n (%)	22 (13.5)	39 (22.4)

*Due to slow recruitment and logistical issues the study had been stopped.

**Consisting of all patients from the Safety Population which had at least one post-baseline assessment of the primary efficacy variable (= efficacy population)

Demographic and Background Characteristics

			Efficacy Population		
			Total	Certoparin	UFH
Variable		Statistic	(N=203)	(N=103)	(N=100)
Age [yrs]		N	203	103	100
		NMiss	0	0	0
		Mean	71.6	71.6	71.7
		Std	11.7	11.2	12.4
		Min	41	44	41
		Median	74.0	74.0	74.0
		Max	94	90	94
	< 73 years	n (%)	88 (43.3)	45 (43.7)	43 (43.0)
	>= 73 years	n (%)	115 (56.7)	58 (56.3)	57 (57.0)
Sex	Male	n (%)	92 (45.3)	45 (43.7)	47 (47.0)
	Female	n (%)	111 (54.7)	58 (56.3)	53 (53.0)
Race	Caucasian	n (%)	203 (100.0)	103 (100.0)	100 (100.0)

Primary Objective Result(s)

Thromboembolic Events (proximal or distal DVT, PE or VTE related death) during treatment

UFH (N=100)	Certoparin (N=103)	Difference			Odds Ratio		
n (%)	n (%)	%	95 % CI	p|Diff=0	OR	95 % CI	p|OR=1
18 (18.0)	11 (10.7)	-7.3	[-16.9 , 2.3]	0.1353	1.8	[0.8 , 4.1]	0.1401
one-sided p-value for the shifted null hypothesis that the difference between treatment groups equals 4%: p= 0.0081							

Secondary Objective Result(s)

Thromboembolic Events (proximal or distal DVT, PE or VTE related death) during follow-up

UFH (N=152)	Certoparin (N=150)	Difference			Odds Ratio		
n (%)	n (%)	%	95 % CI	p|Diff=0	OR	95 % CI	p|OR=1
4 (2.6)	3 (2.0)	-0.6	[-4.0 , 2.8]	0.7150	1.3	[0.3 , 6.0]	0.7162

AEs of Special Interest, occurring during treatment (Safety population)

	Total (N=335) n (%)	UFH (N=172) n (%)	Certoparin (N=163) N (%)
Hemorrhage (major or minor)	8 (2.4)	4 (2.3)	4 (2.5)
Thrombocytopenia	1 (0.3)	1 (0.6)	0 (0.0)
Symptomatic HIT type II	0 (0.0)	0 (0.0)	0 (0.0)
Induction of HIT-II specific antibodies	0 (0.0)	0 (0.0)	0 (0.0)

Safety Results

During treatment:

The most commonly reported overall AEs and by SOC during treatment were “Gastrointestinal Disorders”, “Infections and Infestations”, “Psychiatric disorders ”, “Metabolism and nutrition disorders”, and “Musculoskeletal and connective tissue disorders”.

During follow up:

The most commonly reported overall AEs and by SOC during follow up were “Gastrointestinal Disorders”, “General disorders and administrative site disorders”, “Infections and Infestations”, and “Psychiatric disorders”.

Adverse Events by System Organ Class/preferred term

Number of Patients with AEs with suspected drug relation during treatment

System organ class Preferred term	UFH (N=172)	Certoparin (N=163)
	n (%)	n (%)
All System Organ Classes	10 (5.8)	5 (3.1)
Gastrointestinal disorders	2 (1.2)	0 (0.0)
Duodenal ulcer haemorrhage	1 (0.6)	0 (0.0)
Intra-abdominal haematoma	1 (0.6)	0 (0.0)
General disorders and administration site conditions	1 (0.6)	0 (0.0)
Injection site haematoma	1 (0.6)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	2 (1.2)
Periorbital haematoma	0 (0.0)	1 (0.6)
Post procedural haemorrhage	0 (0.0)	1 (0.6)
Investigations	4 (2.3)	2 (1.2)
Alanine aminotransferase increased	0 (0.0)	1 (0.6)
Hepatic enzyme increased	4 (2.3)	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.6)	0 (0.0)
Pulmonary embolism	1 (0.6)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (0.6)	0 (0.0)
Erythema	1 (0.6)	0 (0.0)
Vascular disorders	1 (0.6)	2 (1.2)
Deep vein thrombosis	1 (0.6)	1 (0.6)
Haemorrhage	0 (0.0)	1 (0.6)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

	UFH	Certoparin
Constipation	13 (7.6)	11 (6.8)
Diarrhoea	15 (8.7)	9 (5.5)
Insomnia	10 (5.8)	6 (3.7)
Vomiting	3 (1.7)	1 (0.6)
Pyrexia	3 (1.7)	2 (1.2)
Hypokalaemia	3 (1.7)	4 (2.5)
Gastrooesophageal reflux disease	3 (1.7)	0 (0.0)
Gastric ulcer	2 (1.2)	0 (0.0)
Gastritis	2 (1.2)	3 (1.8)
Bronchitis	2 (1.2)	2 (1.2)

Serious Adverse Events and Deaths

Number of Patients with SAEs during treatment and follow up

	During core study		During Follow up	
	UFH (N=172)	**Certoparin (N=163)**	**UFH (N=152)**	**Certoparin (N=150)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
All System Organ Classes	14 (8.1)	9 (5.5)	16 (10.5)	11 (7.3)
Cardiac disorders	3 (1.7)	0 (0.0)	3 (2.0)	0 (0.0)
Gastrointestinal disorders	3 (1.7)	1 (0.6)	2 (1.3)	0 (0.0)
General disorders and administration site disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
Infections and infestations	2 (1.2)	1 (0.6)	4 (2.6)	1 (0.7)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.7)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Musculoskeletal and connective tissue disorder	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Neoplasms benign, malignant and unspecified	3 (1.7)	4 (2.5)	2 (1.3)	3 (2.0)
Nervous system disorders	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.7)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	4 (2.5)	2 (1.3)	2 (1.3)
Vascular disorders	1 (0.6)	0 (0.0)	2 (1.3)	0 (0.0)

Number of Patients of Significant Adverse Events during Treatment and Follow up

	During core study		During Follow up	
	UHF (N=172)	**Certoparin (N=163)**	**UHF (N=152)**	**Certoparin (N=150)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
All Adverse Events	96 (55.8)	78 (47.9)	41 (27.0)	26 (17.3)
with suspected drug relation	10 (5.8)	5 (3.1)	6 (3.9)	4 (2.7
leading to dose adjustment or temp. interruption	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
leading to permanent discontinuation	8 (4.7)	7 (4.3)	0 (0.0)	1 (0.7)
requiring concomitant medication/non-drug therapy	75 (43.6)	60 (36.8)	19 (12.5)	17 (11.3)
Serious Adverse Events (SAEs)	14 (8.1)	9 (5.5)	16 (10.5)	11 (7.3)
Deaths	3 (1.7)	1 (0.6)	9 (5.9)	7 (4.7)
SAEs with suspected drug relation	2 (1.2)	1 (0.6)	0 (0.0)	1 (0.7)
SAEs leading to permanent discontinuation	4 (2.3)	3 (1.8)	0 (0.0)	0 (0.0)

Date of Clinical Trial Report

25-Nov-2009

Date Inclusion on Novartis Clinical Trial Results Database

07-05-2010

Date of Latest Update

23-03-2010